The Rising Incidence of Gastric Cardia Cancer

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Recent estimates of global cancer statistics have ranked stomach cancer behind only lung cancer in the number of new cases and deaths worldwide *(1)*. Incidence and mortality rates for stomach cancer in the United States and developed countries of Europe have decreased steadily for many years, while the rates still remain considerably higher in many developing countries *(2–5)*. In the face of the overall decline in stomach cancer, a number of investigators around the world have reported rising incidence rates for gastric cardia adenocarcinoma, almost always in conjunction with increases in esophageal adenocarcinoma *(6–15)*. In the United States, based on data from the Surveillance, Epidemiology, and End Results (SEER)[1] program, incidence rates for both gastric cardia and esophageal adenocarcinomas have increased 4%–10% per year among men since 1976, more rapidly than for any other type of cancer *(6)*. In recent years, the incidence of gastric cardia adenocarcinoma in the United States among white males has nearly equaled the rate for noncardia gastric tumors *(7)*. In Sweden, the incidence of gastric cardia carcinoma since 1970 has shown a mean annual increase of 2.5% *(11)*.

In this issue of the Journal, Ekstrom et al. *(16)* investigate whether variations in the diagnosis, classification, and reporting of gastric cancer in Sweden might have affected the observed increase in the incidence of cardia tumors. They used data from a case–control study in which gastric cancer cases diagnosed from 1989 through 1994 were identified and compared with those routinely reported to the Swedish Cancer Registry. The study procedures included detailed rules for examining medical records and review of all available histologic slides by an experienced pathologist. The distance from the cardioesophageal junction was used to define cancers arising in the gastric cardia *(17)*. Compared with the "gold standard" of information obtained from the case–control study, Ekstrom et al were able to quantify the degree to which gastric cardia adenocarcinomas were misclassified over the time period. In particular, the inclusion of false positives and the missing of true cases in the registry raised concerns that misclassification may have contributed to the upward trends observed for gastric cardia adenocarcinoma *(11)*, even though no variation in misclassification was detected over the relatively short period studied.

According to the most recent volume of Cancer Incidence in Five Continents *(18)*, registration of cancer in Sweden is compulsory for physicians, hospitals, and pathologists, and case registration is estimated to be 96% complete. From 1988 through 1992, 96% or more of all stomach cancers diagnosed and reported to the Swedish Cancer Registry had microscopic verification of the diagnosis, comparable to the best population-based registries in the world. However, a relatively high proportion of cases had gastric tumors that either spanned at least two subsites or were of unspecified origin. This category accounted for 75% of gastric cancers among males and 83% among females. With increasing evidence that cardia and noncardia tumors differ in terms of environmental *(7)* and possibly genetic determinants *(19)*, it seems plausible that diagnostic and reporting practices may have contributed to the observed increase in cardia tumors, but unfortunately the Ekstrom report does not provide data on the corresponding trends for noncardia gastric cancers. Indeed, it is surprising that more gastric cardia tumors were not found after careful record and pathology review, given the high proportion of cases coded to multiple or unspecified subsites. In the United States during the same period from 1988 through 1992, 25% and 32% of the total stomach cancer cases among white males and females, respectively, did not have a precisely designated subsite *(18)*. Of these, more than one third had tumors that overlapped at least two subsites *(20)*. The proportion of all stomach cancers among white males with unspecified subsite decreased from 38% in the 1970s to 29% in the 1980s *(6)*. We have estimated that, if the unspecified gastric tumors were distributed anatomically in proportion to the relative frequencies of adenocarcinoma by known subsite, about one fourth of the observed increase in the incidence of gastric cardia cancer from 1976 through 1987 would have resulted from more specific diagnoses *(6)*. Further work is needed to clarify time trends in gastric cardia and noncardia cancer around the world, but these studies are currently limited by the high proportion of unspecified gastric tumors in many population-based cancer registries *(18)*.

The problem of distinguishing gastric cardia from noncardia adenocarcinomas is further magnified by the difficulty in separating cardia tumors from adenocarcinomas of the esophagus, an issue not addressed in the Ekstrom study. Some case–control studies of esophageal and gastric cardia adenocarcinomas have combined these tumors as a single entity *(21–25)*, whereas others have examined them separately *(26–28)*. Although all of these studies included a review of hospital and pathology records, only Lagergren et al. *(28)* mentioned using distance from the gastroesophageal junction to define cardia tumors. It is interesting that, although three authors of the Lagergren paper are also authors of the Ekstrom report, the definitions used for cardia cancer are different. Lagergren et al. *(28)* included as gastric cardia tumors those tumors having an estimated point of origin within 2 cm proximal or 3 cm distal to the gastroesophageal junction, whereas Ekstrom et al. *(16)* included those tumors centered within 1 cm proximal and 2 cm distal to the junction, citing Misumi et al. *(17)* as the source of their definition. It is questionable whether tumors originating proximal to the junction should be classified as cardia rather than esophageal adenocarcinoma. Thus, it appears likely that the discrepancies in site classification reported by Ekstrom et al. result in part from the diagnostic practices of Swedish clinicians and pathologists in defining tumors of the gastric cardia and in part from the lack of routine reporting of subsites to the cancer registry.

Historically, esophageal cancers were mostly squamous cell carcinomas, whereas stomach cancers were adenocarcinomas *(29)*, with both sites being more common among African-

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Americans than whites in the United States *(30)*. Epidemiologic investigations of stomach cancer have consistently identified dietary factors, such as low intake of fruit and vitamin C, and infection with *Helicobacter pylori* as important risk factors *(5)*, whereas studies of esophageal cancer have implicated cigarette smoking and heavy alcohol consumption as major determinants *(31)*. Evidence is emerging, however, that gastric and esophageal tumors may be classified as at least three distinct etiologic forms of cancer. Although incidence rates for noncardia gastric tumors and (to a lesser extent) esophageal squamous cell carcinomas have steadily declined, the incidence of gastric cardia and esophageal adenocarcinomas has risen in the United States, especially among white males *(6,7)*. The temporal and racial patterns by subsite and cell type are so pronounced that it seems very unlikely that diagnostic and reporting practices play a major role in the rising incidence of gastric cardia or esophageal adenocarcinomas. In addition, recent analytic studies have revealed a similar array of risk factors, with gastroesophageal reflux disease and subsequent Barrett's esophagus as predisposing conditions for both tumors *(23,28)*. Cigarette smoking is also linked to these tumors, although the risks are lower than for esophageal squamous cell carcinoma and persist longer after smoking cessation *(21,22,24,26,32–34)*. In addition, obesity has emerged as an important risk factor *(27,33,35)*, perhaps by increasing intra-abdominal pressure and subsequent reflux disease *(23,36–38)*. Although *Helicobacter pylori* infection plays an important role in noncardia gastric cancer, there is some evidence that cagA+ strains may have an inverse relation to gastric cardia and esophageal adenocarcinomas *(39–42)*. A variety of other risk factors are under active investigation to identify reasons for the upward incidence trends in both tumors.

By their careful study of incidence data for gastric cardia cancer in Sweden, Ekstrom et al. *(16)* have illustrated the need to evaluate the specificity and accuracy of diagnoses in interpreting the rising trend, which corresponds in other populations to marked increases in esophageal adenocarcinoma. With improvements in the quality of data collected by cancer surveillance systems in various countries, it should be possible to limit the potential sources of bias and error, and thus to identify temporal and other patterns of cancer that give rise to etiologic hypotheses.

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NOTE

[1]SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.